

Research

Cancer: a single disease with a multitude of manifestations?

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Abstract

The relationships of critical nutrients such as plant phenolics, vitamins, minerals and lipids are considered with respect to the incidence of a variety of cancers, and analyzed in terms of how these nutrient deficiencies alter immune function, DNA integrity and cell proliferation. With a significant correlation found between cancer and these nutrient deficiencies, the hypothesis is presented here that nutrition could provide a unifying perception of cancer and recast it as a single disease. This further suggests that a coordinated administration of specific, critical nutrients to cancer patients could lead to the reversal of the disease. It is also proposed that the concurrent presence of a variety of nutritional deficiencies in cancer patients requires a multilevel, systemic approach to this disease as opposed to the single active therapeutic agent approach that is the cornerstone of contemporary research and pharmacology.

Introduction

In the 20th century, major structural changes took place in the countries of the developed world. Primarily agrarian societies were transformed into industrial societies with the accompanying migration of the majority of the population into large urban centers. This led to major lifestyle changes with unforeseen consequences. Diet in early 20th century agrarian societies was primarily based on organically produced fresh food. Food production was mainly carried out in relatively small family operations utilizing organic farming methods. By the end of the century, the landscape had completely transformed into large-scale industrial farming, utilizing non-organic production methods along with an industrial processing and distribution system for the majority of essential food items.

Dietary patterns were thoroughly transformed. Data show that per capita energy consumption increased significantly and within that, the fat and animal protein segments more than tripled [1,2]. Although fruit and produce consumption also increased, most of it is not

consumed fresh [3]. Due to widespread food processing, the energy density of our foods also increased [1]. The now commonplace refrigeration and freeze storage removed the need for fresh food prepared daily and allowed the distribution of a wide variety of manufactured food products. These changes did not necessarily lead to a quality improvement in our nutrition. Along with these changes, physical activities decreased which may well have contributed to the now-epidemic proportions of obesity in the Western world.

Environmental factors

Although cancer is primarily considered to be genetically linked, it is now well established that diet has a significant effect on cancer incidence [4-6]. In fact, food consumption patterns could provide major insights into cancer risk and prevention despite the fact that their significance is not fully appreciated [7]. The changes in cancer incidence in migrant populations moving from low cancer incidence to high cancer incidence environments clearly dem-

onstrate that environmental factors are more important than genetics [8,9].

Among the developed countries, Japan continues to exhibit the lowest cancer incidence in the major cancers types, including lung, breast and colon carcinomas, although some cancers have increased in incidence due to the introduction of Western dietary practices [10,11]. Notably, immigrant Japanese in California and Hawaii has a much higher incidence of breast and colon cancer [8,9]. In Japan, the consumption of fresh, raw foods continues to remain important even though in all other aspects (industrialization and urbanization) the Japanese have adapted the Western model. In addition, the Japanese have the same risk factors such as smoking, alcohol consumption and sedentary life styles as Westerners. The only notable exception in risk factors is the relative rarity of obesity in Japan, a difference that is also attributable to dietary customs.

Another line of evidence comes from Australia, demonstrating the increase in colon cancer mortality among immigrant populations originating from low-incidence countries [12]. Similar observations were made in some South Pacific Islander groups where the incidence of lung cancer is extremely low despite high rates of smoking [13]. Over the past decades, population-based approaches have identified food classes or nutrients that confer protection from various cancers or enhanced the risk of cancer [14-17]. In fact, there is evidence that dietary manipulations may be protective against 10–70% of all cancers, and may be as high as 50–70% against colon cancer [18,19].

Plant phenolics

Epidemiological studies implicated high-saturated dietary fat and protein as a risk factor for colon cancer and established that high fiber, high fruit and vegetable content are protective [17,18]. The success of the dietary fiber hypothesis [20,21] is particularly intriguing in light of the recognition that the actual protective agent is not the fiber itself, but the cell wall components, phenolic polysaccharides and polyphenols [22-27]. The protective phenolic lignin and hemicellulose components are present in widely different concentrations in the cell walls of various plants and are released by bacterial enzymes in the human colon [23]. Such compounds have been isolated, e.g. from rice bran and green tea, and their cancer protective effects demonstrated [24,25,27]. Processed rice bran, however, had no such protective effect [28]. Many of these compounds have antioxidant, anti-mutagenic, anti-carcinogenic and anti-inflammatory effects that may be responsible for their anticancer effects [29].

A readily available source for such phenolic polysaccharides can be located in the nutritional and medical prac-

tices of the 19th and early 20th centuries [30,31]. Sugar cane molasses, a widely used nutrient, was served as a sweetener instead of purified sugar, stirred into milk and eaten instead of jam or jelly. It was also a popular medicinal agent: recent analyses demonstrated it to be a rich source of micro- and macronutrients [32]. Blackstrap molasses, its most concentrated form, was used for the therapy of a variety of diseases, including cancer [31]. Anecdotal evidence suggests that cancer was very rare among sugar cane plantation workers who were regularly consuming the raw brown sugar [33]. Blackstrap molasses is rich in a variety of essential minerals including iron, zinc, selenium, magnesium and potassium as well as the majority of the vitamin B complex [33], deficiencies of which confer a major cancer risk [34]. Molasses also contains high concentrations of amino acids and linoleic acid [35], an essential lipid that has a documented anti-tumor effect [36,37].

Cane molasses is fed widely to domestic animals [35]. A feeding study on the phenolic carbohydrate compounds of cane molasses suggested that they are beneficial to both ruminant and non-ruminant animals [38]. The feeding of 8% sugar cane bagasse to broiler chicken demonstrated weight gain and carcass quality as well as elevated immunoglobulin levels [39]. Recent data on cane molasses appear to lend support to historical accounts concerning its effectiveness as both preventative and a possible curative agent for some cancer.

Folate, vitamin B12 and other micronutrients

In the past decade it became apparent that low normal levels of certain vitamins may cause diseases in at-risk populations, such as middle to elderly age groups and pregnant women, and that such abnormalities might be overcome by ensuring high normal plasma levels of the respective vitamins [40-42]. Metabolic defects of folate are associated with circulatory diseases [43,44] as well as neural and cognitive disorders [45]. Folate deficiency has recently been associated with pathogenesis in a variety of malignancies [46-50]. The most understood functions of folate and vitamin B12 are in the area of synthesis of purines and pyrimidines, as well as the maintenance of the methylation process that is essential for regulated cell division [51].

Several lines of evidence, both *in vitro* and *in vivo*, suggest that folate deficiency has pro-neoplastic effects. Deoxynucleotide pool imbalance and uracil misincorporation into DNA in folate deficient cell lines has been described [52,53]. Enhanced development of colonic neoplasia was observed in a folate-deficient rat model [54,55]. Several human studies demonstrate that folate deficiency may potentiate neoplastic processes and that high dietary folate intake is protective [46-50,56]. It is well established

that folate deficiency leads to nucleotide pool imbalance (uracil misincorporation), DNA strand breaks [57,58], hypomethylation of DNA [59-61], increased gene expression [62-64], altered chromatin conformation [63,64], as well as altered cellular proliferation [62,67]. All these phenomena have been associated with carcinogenesis and tumorigenesis.

It has been recommended that patients undergoing chronic methotrexate or other antifolate therapy increase folate intake [68]. In such cases, high dose of folic acid (5 mg/day) have reduced therapy-associated toxicity with apparent preservation of antitumor activity [69]. This supports the view that antifolates act through a direct cytotoxic mechanism [70].

There is a close interrelationship between folate and vitamin B12 in the synthesis, repair and methylation of DNA. In a human clinical trial, a three-month-long supplementation with 3.5 times the Australian Recommended Daily Allowance (RDA) for folic acid and vitamin B12 was found to reduce micronuclei frequency, a DNA damage marker, in healthy young adults by 25% [71]. This study emphasized that supplementation levels higher than the RDA may be required in large populations to minimize DNA damage. Our RDAs were based on information on acute effects, because optimum amounts for long-term health is unknown. However, these data suggest that RDA levels may need to be reevaluated to make sure that adequate levels of these nutrients are available for genomic stability.

Supplementation with folic acid and vitamin B12 has reduced the severity of smoking-induced bronchial metaplasia in humans [72,73], underscoring the importance of these vitamins. Folate and vitamin B12 deficiencies that lead to chromosome breaks affect a significant 10–14% of the U.S. population [74-77]. The two deficiencies may act synergistically. Vitamin B6, which also participates in DNA methylation, was also found to be deficient in about 10% of the U.S. population [76].

Besides the above micronutrients, niacin, iron, selenium and zinc deficiencies that also affect DNA integrity are common in the United States [76,78]. All these data suggest that micronutrient deficiencies, which can mimic radiation or chemical damage to DNA, are affecting a considerable proportion of the U.S. population, and the correction of these deficiencies will be a major public health concern in the coming decades.

Iodine

Iodine is another critical micronutrient, and iodine deficiency has a profound effect on human health [79,80]. Mild to moderate iodine deficiency has been associated

with an extraordinarily high occurrence of hyperthyroidism in at-risk populations [81]. Epidemiological studies have established that the incidence of goiter runs parallel to that of thyroid cancer [82-84]. In a rat model, iodine deficiency has been found to be a more efficient tumor promoter than the carcinogen itself [85].

The relationship between thyroid function and breast physiology was strengthened by observations that reproducible breast dysplasia and neoplasia were obtained in iodine deficiency that was reversible with iodine replacement [86,87]. Breast cancer patients as a group were found to have a lower thyroid function than women having conditions unrelated to breast cancer [88].

It has been pointed out that in the U.S., breast cancer tends to occur in geographical areas associated with iodine deficiency [89]. In contrast, in Japan, where iodine intake levels are higher, a much lower breast cancer incidence is observed [90]. Fibrocystic breast disease, a known risk factor for breast cancer, can largely be prevented by iodine supplementation [91]. In this study, molecular iodine was found to be more effective than iodide, the currently favored form of iodine supplementation. In iodine supplementation studies unrelated to cancer, molecular iodine complexed to lipids was also found to be more effective than iodide [92]. It was also reported that iodolipids formed from iodine in the thyroid gland may play a role in providing proliferative control in breast tissue [93]. Another observation is that in old Pharmacopoeias, for oral iodine administration the molecular form was prescribed [94].

While breast cancer rates in Japan have been comparatively low, they have been increasing recently: this has been associated with the "Westernization" of the country's diet [11]. A study from Spain also established a link between regions of iodine deficiency and breast cancer mortality rates [95]. Traditional Eastern Asian medicine has long used iodine-rich seaweed for cancer treatment [96]. This observation is interesting in light of the fact that in malignant thyroid nodules, the iodine concentration was found to be 15 times lower than in benign nodules [97], demonstrating severe iodine deficiency in the tumor tissue. Recent studies with animal models support the anti-cancer effect of iodine [98,99].

Iodine deficiency has a profound negative effect on the immune system [100]. A significant immune deficiency has been reported among patients with gastric cancer, thyroid cancer and goiter [101]. Iodine was also found to increase immunoglobulin G synthesis *in vitro* in human lymphocytes [102]. Impaired capacity of immunoglobulin production in active cancer patients has been observed [103], which might be modulated by iodine supplemen-

tation. These observations indicate that iodine has a direct effect on the immune system and anticancer defenses.

In 1990, statistics showed that iodine deficiency affected about one-third of the world's population, and despite efforts to correct this problem, it persists. A recent study from South Africa indicated a significant iodine deficiency country-wide [84]. Another study from Switzerland reported that despite more than 80 years of a national iodine supplementation program, only 24% of the participants in the healthy volunteer group reached the WHO recommended level for dietary iodine intake, indicating a significant iodine deficiency among the Swiss [104]. This result was attributed to the growing consumption of manufactured food products deficient in iodine. Although similar data is not available for the United States, a comparable level of development and the high popularity of manufactured foods suggest that the US situation is likely not much different from that in Switzerland.

Lipids

It has been previously discussed that the essential lipid linoleic acid present in cane molasses has antitumor effects. Such lipids are also found at high concentrations in rose oil [105], which has a history of medicinal use dating back at least 5,000 years. The traditional Indian Ayurvedic medical practice uses oral rose oil for the treatment of a variety of inflammatory conditions, as well as emotional stress [106]. Anti-anxiety effects of rose oil have recently been confirmed [107]. Rose oil is a potent inhibitor of the growth of *Helicobacter pylori* [108], implicated in the etiology of gastric cancer. Therefore, rose oil may exert a "sanitizing" effect in the gut. It has also been suggested that rose oil may be valuable for human consumption because of its high unsaturated lipid content [105].

The gastrointestinal link

The general processing capacity of the digestive tract plays a critical role in both health and disease. Traditional Indian Ayurvedic medicine states that health requires robust digestion [109]. Under conditions of prolonged stress, the secretion of digestive juices is diminished, reducing the digestive capacity in the gut.

Impaired digestion has been implicated in the pathomechanism of cancer for nearly a century: in 1906, pancreatic proteolytic enzymes were demonstrated to defend the body against cancer [110]. This finding was followed up during the first decade of the century, with the publication of tumor regression as well as remission in terminal cancer patients [111-114]. With the advent of formal science-based medicine in the early 1900s, this approach slipped into oblivion.

Animal studies performed in the 1960s demonstrated the effectiveness of pancreatin therapy for tumors [115,116]. It was also demonstrated that orally ingested pancreatic enzymes pass intact into the intestine, and are re-adsorbed into the circulation during the enteropancreatic recycling process [117,118]. In the 1960s, an alternative physician in Texas developed a pancreatin-based cancer therapy [119] and demonstrated cases of pancreatic cancer patients who survived in excess of 5 years. This was followed up in the late 1990s by a pilot prospective case study with patients having inoperable stage II-IV pancreatic adenocarcinoma [120]. The results suggested a significantly increased survival for patients who received large doses of pancreatic enzymes, vitamins and minerals followed by the detoxification of the intestines. Many medical practitioners in the past included intestinal cleansing as part of their procedures because they recognized the importance of the gut function in health and disease [121-123].

The resident bacterial flora in the digestive tract plays an important role in metabolic activities, nutrient adsorption, immune function, trophic effects on the intestinal epithelia, and protection against alien microbes [124]. A substantial portion of these bacterial populations remains to be described. Diet has a significant effect on the human intestinal flora [125,126], and the promoting effects of the large bowel contents in colonic carcinogenesis are documented both in animal models and man [127]. The activity of colonic bacteria in the release of essential phenolic polysaccharides from plant cell walls has been discussed. Opportunistic bacterial and parasitic infections also occur in cancer [128-131] that amplify the downward spiral of diminishing nutrient processing capacity of the gut. It is therefore critical to cleanse the digestive and excretory system in cancer patients.

Again, if we research the medical practices of the 19th and early 20th centuries, we find that oral sulfur was widely used to "clean out the system" [31]. Sulfur is safe to consume [132] and has a wide spectrum of antibacterial and antiparasitic effects [133]. It is also a potent scavenging agent for toxic heavy metals such as mercury, cobalt or silver that have been reported to concentrate in malignant tissue [97]. Oral sulfur was listed in the Pharmacopoeia [133], but in the second half of the 20th century its medical use was abandoned. Another sanitizing agent both for the gut and the urinary system is apple cider vinegar (ACV). Such use of ACV has a historical record dating back over 3,000 years [134]. In addition, ACV has been used for the treatment of a number of specific conditions [134], which suggests that it has a beneficial systemic effect, much of it remains to be re-discovered by methods of modern medical science.

Subtle energetic properties of nutrients

A subtle energetic aspect of nutrients is a concept that is largely missing from modern nutritional sciences. We are all familiar with the different feeling experienced when consuming a freshly picked fruit versus a stale one that has been sitting for weeks on the shelves of a food distribution outlet. Some Asian cultures attribute such subtle energetic characters to nutrients, e.g., the yin and yang that is related to chi, the life energy believed to animate every living thing. With our food we consume this energy, which enhances its nutritional value. Freshness of food is emphasized in these cultures, as the life energy is gradually lost after harvest. The consumption of raw, fresh foods in Japan has already been correlated with a low incidence of the major forms of cancer.

This concept was impossible to subject to modern scientific analysis until Wilhelm Reich proved experimentally the existence of a life energy field that is not electromagnetic in nature, but can produce thermal and electric effects in a well reproducible and quantifiable manner [135]. A recent academic study has confirmed Reich's basic findings [136,137]. The incorporation of his methodologies into our working knowledge base could add an exciting new dimension to nutritional science, as we may finally be able to quantify "what health is" and definitively establish what kind of nutrient intake is required for long term health.

Reich also made fundamental contributions to understanding the emotional aspects of the disease process and in particular cancer that he determined to be a manifestation of subtle energetic processes in the body [138]. We are now aware that emotional stress down-regulates the immune system and makes people more prone to cancer [139-142]. Reich's analysis of the subtle energetic processes in cancer patients and their relationship to those emotional blocks makes his research perhaps the most original and intriguing area of study in the history of 20th century medical science.

Although Reich was occasionally skeptical about a possible unification of his subtle energy-based approach to cancer versus our mechanistic, physico-chemical approach, there seems to be no conflict between these methodologies, and instead I suggest that they merely represent different observational levels of the same reality. The unification of a subtle energetic description of disease processes with our current mechanistic, physico-chemical approach is both inevitable and necessary to solving the mysteries of degenerative diseases such as cancer, which claim so many lives today.

Overcoming tumor adaptation

Acquired drug resistance is a common problem with metastatic cancers, contributing to the deaths of more than 450,000 patients annually in the US [143]. A tumor may respond initially to therapy but recur later with acquired drug resistance, or exhibit an intrinsic resistance from the outset. Multidrug-resistance (MDR) manifests through an ATP-dependent drug efflux pump, the P-170 glycoprotein or MDR pump [144]. Quinine has been found to reverse MDR in a variety of tumor cell lines and has been safely used in combination with chemotherapy with leukemias, myelomas and lymphomas [145-147]. Very little information is available on direct cytotoxic effects of quinine [148].

Quinine has a history in medicine besides its use as an anti-malarial. Quinine was used to treat inflammations and fevers [149] and was prescribed as a body tonic to strengthen the system [149,150]. The beverage Tonic Water has preserved in its name the long-forgotten medicinal origins of quinine. However, the concentration of quinine in Tonic Water today is too low for any beneficial systemic effect. Therefore, the use of quinine in cancer may be warranted both for its anti-inflammatory properties as well as its inhibitory effect on tumor adaptation to therapies.

Discussion

This review has considered several critical nutrient deficiencies that may contribute to the manifestation of a number of cancers, as well as nutrients that have been found deficient in cancer cells. It is also observed that traditional nutritional and medicinal agents used in the past provided a rich supply of these critical nutrients and assisted in the restoration of digestive and excretory functions. Again, blackstrap molasses is a source of plant phenolic compounds, the majority of the vitamin B complex, critical minerals such as iron, zinc, selenium, magnesium and potassium, as well as essential unsaturated lipids.

Rose oil is another historically proven source of essential lipids. Our current understanding on the vital role of folate and vitamin B12 in maintaining DNA integrity and function should prompt us to reevaluate dietary requirements for these essential vitamins. Iodine deficiency, which has been demonstrated in cancer, was also shown to impair the immune system and increase the incidence of several cancers. The disinfecting effects of oral sulfur and apple cider vinegar in the gut and the urinary system help restore digestive and excretory functions, a cornerstone of early medical practice.

A large number of studies demonstrate the inadequacy of Western dietary habits for supplying adequate amounts of critical nutrients and also demonstrate the fundamental

role of nutrition in disease prevention and control. Hippocrates, the father of modern medicine stated, "Your food shall be your medicine and your medicine shall be your food." Currently, both in the public and the scientific community are lacking in their attention to the effects of multiple nutritional deficiencies on the human organism.

It seems reasonable to conclude that a number of coincidental critical nutritional deficiencies can lead to and co-exist in the state of cancer. Disregulation of numerous regulatory and metabolic pathways may occur at multiple levels, eventually leading to the disintegration of metabolic and regulatory networks in terminal cancer. This suggests that cancer is a systemic disease, and that a tumor is likely a late-stage effect rather than the cause of the disease itself. It also explains why cancer typically recurs after the eradication of individual tumors. Therefore, focusing on the cancer cell cannot lead us to understanding the fundamentals of the disease. Here, the results speak for themselves.

It appears unrealistic that we can successfully intervene into this vast out-of-balance network of physiological processes with single active agent therapies and restore balance and health. The time has arrived to abandon one-dimensional thinking and consider the human organism more like a matrix or interconnected system, instead. The large body of available data on metabolic and regulatory processes coupled with methods of information technology should allow us to establish correlations between apparently distant molecular, cellular and physiological events. This would bring a true paradigm shift in our approach to understanding and treating diseases.

The old-time medicinal use of blackstrap molasses, apple cider vinegar, oral sulfur and molecular iodine, rose oil and quinine testifies to a remarkable understanding of human physiology by our ancestors. Such nutritional approach allows a unifying perception of cancer that could recast it as a single disease. This would also suggest that all cancers may arise out of a common cellular/physiological event and, in fact, new evidence points into this direction.

Cancer stem cells for leukemias [151], brain cancer [152] and breast cancer [153] have been described lending support to the 40 years old idea that all cancers may originate from a common progenitor. Thus, evidence is accumulating in support of the view that cancer may actually be a single disease and, as such could be treated by a single therapy.

Our working hypothesis was that by re-supplying critical nutrients to cancer patients in an oral nutritional supplement cocktail and simultaneously cleansing the digestive

and excretory systems by using the described methods of past centuries of medicine, we might cure a wide range of or perhaps all types cancers. Essential ingredients of the supplement include blackstrap molasses, apple cider vinegar, sulfur, quinine, rose oil, folic acid, vitamin B12 and molecular iodine [patent pending]. This supplement is currently being tested in a variety of stage III-IV cancer patients refractory to current therapies.

In conclusion, this paper presents the case that multiple, concurrent nutritional deficiencies may play a fundamental role in tumorigenesis and suggests that the disease process could be reversed by re-supplying the required nutrients in adequate amounts. In addition, a new approach to cancer is advocated that would unify our traditional mechanistic, physico-chemical methodologies with subtle energy-based concepts, under the umbrella of contemporary rigorous scientific testing methods.

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